IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Frank A. Skraly and Martha Sholl

Serial No.: 09/909,574 Art Unit: 1652

Filed: July 20, 2001 Examiner: Yong D. Pak

For: *PRODUCTION OF POLYHYDROXYALKANOATES FROM POLYOLS*

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1-4 and 6-10 in the Office Action mailed March 22, 2007, in the above-identified patent application. The Board has jurisdiction under 35 U.S.C. § 134(a). The Examiner entered a final rejection on March 22, 2007, setting a three-month period for response. The time for responding to the final rejection without a petition for an extension of time expired on June 22, 2007. A response to the final office action was filed on June 22, 2007 together with a Notice of Appeal. The time for filing an appeal brief is two months after filing a Notice of Appeal. Bd.R. 41.37(c). The time for filing an appeal brief without an extension of time expires August 22, 2007.

A first Notice of Appeal and fee was filed on December 22, 2005, a first Appeal Brief and fee was filed February 17, 2006; and a substitute Appeal Brief was filed June 5, 2006. A second Notice of Appeal was filed on June 22, 2007. Appellants request credit for payment of

the original fees for the appeal. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is Metabolix, Inc., Cambridge, MA.

(2) RELATED APPEALS AND INTERFERENCES

This case was previously on appeal. A first Notice of Appeal was filed on December 22, 2005. An Appeal Brief was filed February 21, 2006. The Examiner re-opened prosecution on the merits and issued an Office Action on August 25, 2006. There are no other related appeals or interferences known to appellants, the undersigned, or appellants' assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS

Claims 1-4 and 6-10 are pending and on appeal. Claims 5 and 11-23 have been cancelled. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment and Response filed June 22, 2007. In an Advisory Action mailed on July 30, 2007, the Examiner indicated the amendment would be entered for purposes of appeal. An appendix sets forth the claims on appeal.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 defines a method for producing polyhydroxyalkanoates comprising providing bacteria, plants, and yeast (see at least page 5, lines 18-21), which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase (see at least page 5, lines 1-5), wherein the organisms are genetically engineered to express enzymes (see at least page 3, lines 15-18), which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase (see at least page 4, lines 2-3, page 5, line 18 to page 6, line 28 and Examples 4 and 6), which can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate (see at least page 2, line 22 to page 3, line 6 and claims 11 and 21 as originally filed), and culturing the organisms under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da (see at least claims 1 and 11 as originally filed, page 4, lines 14-16 and the Examples). Claim 10 defines the system for use in the method.

Dependent claims 2, 3, 4, 6 and 7 define the diol as 1,6-hexanediol, 1,5-pentanediol, 1,4-butanediol, 1,2-ethanediol and 1,2-propanediol, respectively and the hydroxyalkanoate monomer as 6-hydroxyhexanoate, 5-hydroxyvalerate, 4-hydroxybutyrate, 2-hydroxyethanoate and 2-hydroxypropionate (see at least page 2, line25 to page 3, line 3). Dependent claim 8 defines the method of claim 1 wherein the organism expresses polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase (see at least page 4, lines 2-3). Dependent claim 9 defines the method of claim 8 wherein the organism is selected from the group consisting of *Escherichia coli*, *Ralstonia eutropha*, *Klebsiella* spp., *Alcaligenes latus*, *Azotobacter* spp., and *Comamonas* spp. (see at least claim 9 as originally filed, page 1, lines 16-21, page 3, lines 18-22, page 5, lines 6-7 and page 6, lines 13-17).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are:

(1) whether claims 1-4 and 6-10 are non-obvious as required by 35 U.S.C. § 103(a) over Skraly, Polyhydroxyalkanoates Produced by Recombinant E. coli, Poster Engineering Foundation Conference: Metabolic Engineering 1998 ("Skraly"), Madison, et al. Metabolic engineering of poly(3-hydroxyalkanoates): from DNA to plastic. Microbiol. Mol. Biol. Rev. 63(1):21-53 (1999) ("Madison") and BRENDA database ("Brenda database").

(7) ARGUMENT

Statement of Facts

Claims 1-4 and 6-10 are rejected under 35. U.S.C. § 103(a) as obvious in view of Skraly, Polyhydroxyalkanoates Produced by Recombinant E. coli, Poster Engineering Foundation

Conference: Metabolic Engineering 1998 ("Skraly"), Madison, et al. Metabolic engineering of poly(3-hydroxyalkanoates): from DNA to plastic. Microbiol. Mol. Biol. Rev. 63(1):21-53 (1999) ("Madison") and BRENDA database ("Brenda database").

Scope and Content of the Prior Art

Skraly

Skraly is poster presentation that discloses engineering specific polyhydroxyalkanoate (PHA) polymers (Skraly, p. 1 and 3). Monomers are fed to recombinant bacteria to produce compositions such as PHB-co-2HB (Skraly p. 6). Page 8 discloses an enzymatic pathway for converting 1,2-propanediol into propionyl-CoA. Page 9 discloses that propionyl-CoA must be converted into 3-hydroxy-valeryl-CoA before it can be polymerized into PHB-co-3HV.

Skraly does not disclose or suggest recombinant organisms that can convert diols into 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate.

Skraly does not disclose or suggest recombinant organisms that can polymerize 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da (Advisory Action mailed July 30, 2007, paragraph bridging pages 3-4)..

Madison

Madison is cited by the Examiner to support the proposition that one of skill in the art can engineer organisms expressing genes necessary to produce PHA.

BRENDA Database

The BRENDA database printout discloses several microorganisms and lists some reactions they are capable of performing including, for example, converting 1,4-butanediol to 4-hydroxybutanal (BRENDA, p. 2) and propane-1,2-diol to 2-hydroxypropanal (BRENDA, p. 3). Pages 10-11 list citations to references that disclose various reductases expressed by microorganisms. Page 11 discloses a citation to a reference describing the cloning and sequencing of the *dhaT* gene of *Klebsiella pneumoniae*.

Rejections Under 35 U.S.C. § 103

Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459 (1966). This standard was recently affirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

The Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

> "The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each

element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. . . . There is no necessary inconsistency between the test and the *Graham* analysis."

"Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986). "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." *In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988).

The Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."

(*KSR*, 127 S. Ct. at 1742, citing *Graham* , 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting M*onroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6th Cir. 1964))).

References relied upon to support a rejection under 35 U.S.C. § 103 must provide an enabling disclosure, i.e., "they must place the claimed invention in the possession of the public." *Application of Payne*, 606 F.2d 303, 314, 203 U.S.P.Q. 245 (C.C.P.A. 1979); *see Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 13 U.S.P.Q.2d 1301 (Fed. Cir. 1989). A publication that is insufficient as a matter of law to constitute an enabling reference may still be relied upon, but only for what it discloses. *See Reading & Bates Constr. Co. v. Baker Energy Resources Corp.*, 748 F.2d 645, 651-652, 223 U.S.P.Q. 1168 (Fed. Cir. 1984); *Symbol Technologies, Inc. v. Opticon, Inc.*, 935 F.2d 1569 (Fed. Cir. 1991).

Analysis

1. Claim 1 is Nonobvious in view of the Prior Art

Claim 1 recites:

A method for producing polyhydroxyalkanoates comprising

providing organisms selected from the group consisting of bacteria, plants, and yeast,

which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase,

wherein the organisms are genetically engineered to express enzymes, which are active in bacteria or plants, selected from the group consisting of ***diol oxidoreductase and aldehyde***

dehydrogenase, wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of **4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate**, and

culturing the organisms under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

As is clear from the discussion in the application, the references cited therein, and the prior art cited by the examiner, production of PHAs in genetically engineered bacteria and plants is known. This has been described in the literature since 1987 for bacteria and 1989 for plants. However, what is described in the prior art is the engineering of organisms with the β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase, using known pathways. Appellants have spent years building on this knowledge to create systems that produce PHAs but from cheaper monomers. In the field of biodegradable plastics produced from alternative non-petroleum sources, cost is a major factor. Unless one can make the PHAs in a cost effective manner, there is no commercial market. It was in this context that appellants identified alternative pathways to provide substrates for the PHA synthase to form PHAs. Only when one started from cheap available substrates, determined a pathway to produce the necessary monomers that could be utilized by the PHA synthase, could one know what enzymes must be expressed by the engineered organisms. However, with this knowledge in hand, it was routine to

identify enzymes having the appropriate specificity for the cheap substrates which would in turn yield the required monomers.

Skraly does not disclose a system that can convert diols into hydroxyalkanoate monomers selected from the group consisting of **4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate.** Skraly discloses the production of comonomer P3HB-co-3HP from glycerol and comonomer P3HB-co-3HV from 1,2-propanediol.

The Examiner points to page 6 to show that Skraly discloses using monomers including 5-hydroxyvalerate and 4-hydroxybutyrate to produce PHAs.

However, the issue is not the monomers. The issue is whether or not the prior art teaches the selection of the enzymes to engineer the organisms to utilize the cheap diol substrates to produce the monomers. Skraly fails to disclose or suggest genetically engineering the microorganism to express enzymes that can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate. Skraly instead provides the monomers as substrates.

The claims require:

"wherein the organisms are genetically engineered to express enzymes, which are active in bacteria or plants, selected from the group consisting of ***diol oxidoreductase and aldehyde dehydrogenase,***

wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of **4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate"**

Thus, Skraly fails to disclose or suggest each element of the claims.

Page 8 of Skraly discloses that 1,2-propanediol is enzymatically converted into propionyl-CoA and that glycerol is converted into 3-hydroxypropionyl-CoA in microorganisms. Page 9 of Skraly discloses that proprionyl-CoA converted to 3-hydroxypropionyl-CoA. 3-hydroxypropionyl-CoA is not claimed. The examiner therefore concludes that one could read into the disclosure that other diols could be utilized, but no evidence for such a conclusion is found in the reference, much less what enzymes would be required and whether they would have the appropriate specificity. There is no basis to conclude that one would genetically engineer the organisms as appellants have done, make the substitutions in feedstock that appellants have done, to produce the claimed polymers, based on this disclosure. Indeed, it was two years later that appellants, who worked with Skraly, et al., filed this application, having isolated the necessary materials, engineered the cells and demonstrated that it was possible.

Madison does not make up for the deficiencies in Skraly. Indeed, the Examiner admits that Madison is cited merely as showing that one skilled in the art could engineer microorganisms to produce PHAs. No where is there any teaching that one could or should make a high molecular weight PHA from diols converted into the claimed monomers by genetically engineering organisms so they could convert the diols into the necessary substrates.

The examiner has not even identified where such polymers are described. Even as to the molecular weight range, this is not for polymers of the claimed monomer composition, but for conventional PHB polymers.

The Brenda database does not make up for the deficiencies of Skraly and Madison. The Examiner cites to Brenda to show that the genes for specific diol reductases were known in the art. Indeed, the genomes of several organisms have been cloned and sequence. The fact that an enzyme has been cloned and sequenced does not provide motivation to one of ordinary skill in the art express that gene in combination with any other gene simply because it is possible to do so. Nor does it lead one to have a reasonable expectation of success.

Appellants have told those skilled in the art how to practice their claimed method; the standard is not whether having the answer in hand one can support the conclusion. This is the examiner's approach, however. Such an approach is impermissible hindsight. The prior art does not teach that one can genetically engineer organisms to utilize diols as a cheap feedstock to make PHAs; the prior art teaches that one must provide the monomers. The prior art does not teach the alternative pathways to PHAs that is required to arrive at the claimed method and organisms.

One also cannot just "lump" the claims together, focusing solely on the elements in the independent claims, and completely fail to examine the elements of the dependent claims. This is as unacceptable as using hindsight.

The Examiner alleges that one of ordinary skill in the art would have a reasonable expectation of success because Skraly teaches a method of producing PHAs from a diol using a

diol reductase/aldehyde dehydrogenase, Madison et al. teaches expression of genes necessary for PHA synthesis, and BRENDA teaches several diol reductases that have been cloned into *E. coli.* It is well known that biotechnology is an unpredictable technology. See *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 42 U.S.P.Q.2D 1001 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 52 U.S.P.Q.2D 1129 (Fed. Cir. 1999). One cannot simply string several genes together like toy blocks and expect a complex metabolic pathway to work in a living organism. First, the art fails to define the required pathway. Second, Skraly acknowledges that the comonomer PHB-co-3HV is more difficult to produce because propionyl-CoA must be converted to 2-hydroxy-valeryl-CoA by a ketothiolase. Absent the guidance provided in Appellants' application, one of ordinary skill in the art would not be able to successfully do that which Appellants have done without engaging in undue experimentation. There are numerous genes encoding any number of diol reductases. Absent appellants' teaching, one of skill in the art would engage in undue experimentation because of the large the number of enzymes that could possibly be used and the large number of combinations of enzymes that are possible. The skilled artisan would need to engineer an incredible number of organisms in the hope of arriving at a recombinant organism expressing a combination of genes and enzymes that produce the polymers recited in the claims.

2. Claim 2 is Nonobvious In View of the Prior Art

The combination of the cited references fails to disclose or suggest each element of claim 2. None of the specific diols and monomer compositions such as 1,6-hexanediol and the

hydroxyalkanoate monomer 6-hydroxyhexanoate of claim 2 are described in the prior art cited by the examiner.

3. Claim 3 is Nonobvious In View of the Prior Art

The combination of the cited references fails to disclose or suggest each element of claim 3. None of the specific diols and monomer compositions such as 1,5-pentanediol and the hydroxyalkanoate monomer 5-hydroxyvalerate of claim 3 are described in the prior art cited by the examiner.

4. Claim 4 is Nonobvious In View of the Prior Art

The combination of the cited references fails to disclose or suggest each element of claim 4. None of the specific diols and monomer compositions of claim 4 such as 1,4-butanediol and the hydroxyalkanoate monomer 4-hydroxybutyrate are described in the prior art cited by the examiner.

5. Claim 6 is Nonobvious In View of the Prior Art

The combination of the cited references fails to disclose or suggest each element of claim 6. None of the specific diols and monomer compositions of claim 6 such as 1,2-ethanediol and the hydroxyalkanoate monomer 2-hydroxyethanoate are described in the prior art cited by the examiner.

6. Claim 7 is Nonobvious In View of the Prior Art

The combination of the cited references fails to disclose or suggest each element of claim 7. None of the specific diols and monomer compositions of claim 7 such as 1,2-propanediol and

the hydroxyalkanoate monomer 2-hydroxypropionate are described in the prior art cited by the examiner.

7. Claim 8 is Nonobvious In View of the Prior Art

Claim 8 depends form claim 1 and further defines the method of claim 1 as having the organism express polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase. The cited references do not disclose or suggest a method for producing polyhydroxyalkanoates using organisms that express polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase that can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, and wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

8. Claim 9 is Nonobvious In View of the Prior Art

Claim 9 depends from claim 8 and further defines the organism as selected from the group consisting of *Escherichia coli*, *Ralstonia eutropha*, *Klebsiella* spp., *Alcaligenes latus*, *Azotobacter* spp., and *Comamonas* spp. The cited references do not disclose or suggest a method for producing polyhydroxyalkanoates using *Escherichia coli*, *Ralstonia eutropha*, *Klebsiella* spp., *Alcaligenes latus*, *Azotobacter* spp., or *Comamonas* spp. that express polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase that can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-

hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, and wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

9. Claim 10 is Nonobvious In View of the Prior Art

Claim 10 defines a system for making polyhydroxyalkanoates using organisms selected from the group consisting of bacteria, plants, and yeast , which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase, wherein the organism is genetically engineered to express polynucleotides that encode enzymes, which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase, wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, wherein the monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

As discussed above, Skraly does not disclose a system that can convert diols into hydroxyalkanoate monomers selected from the group consisting of **4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate.** The only monomers that

Skraly describes using are 3-hydroxybutyrate and 3-hydroxypropionate to make P3HB-co-3HP and 3-HB and 3-hydroxyvalerate to make P3HB-co-3HV. None of these are claimed. Skraly does not tell one how to engineer the organisms, with what enzymes, nor the requisite pathways to get to the intermediates to make PHAs. The examiner has drawn conclusions that one could read into the disclosure that other diols could be utilized, but no evidence for such a conclusion is found in the reference, much less what enzymes would be required and whether they would have the appropriate specificity. There is no basis - other than impermissible hearsay - to conclude that one would make the substitutions in feedstock that appellants have done, to produce the claimed polymers, based on this disclosure.

Madison does not make up for the deficiencies in Skraly. Indeed, the Examiner admits that Madison is cited merely as showing that one skilled in the art could engineer microorganisms to produce PHAs. No where is there any teaching that one could or should make a high molecular weight PHA from diols converted into the claimed monomers. The examiner has not even identified where such polymers are described. Even as to the molecular weight range, this is not for polymers of the claimed monomers, but conventional P3HB polymers.

The Brenda database does not make up for the deficiencies of Skraly and Madison. The Examiner cites to Brenda to show that the genes for specific diol reductases were known in the art. Indeed, the genomes of several organisms have been cloned and sequence. The fact that an enzyme has been cloned and sequenced does not provide motivation to one of ordinary skill in

the art express that gene in combination with any other gene simply because it is possible to do so.

In summary, the prior art neither discloses the claimed elements nor the motivation to combine as appellants have done, much less with a reasonable expectation of success.

Conclusion

The prior art fails to teach each of the claimed elements, and in particular:

organisms genetically engineered to express diol oxidoreductase and/or aldehyde dehydrogenase in bacteria, yeast or plants

which can convert diols into 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, or 3-hydroxyhexanoate

which are cultured under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

The prior art fails to teach the problem to be solved and a pathway that could be used to solve the problem, i.e., utilization of cheap diol substrates to make PHAs from defined monomers.

The prior art fails to suggest selecting from among the myriad enzymes that one could select from and feedstocks, to make the desired polymers, absent hindsight, without undue experimentation.

Accordingly, the prior art does not make obvious the methods and compositions of claims 1-4 and 6-10.

Respectfully submitted,

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Date: August 22, 2007

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(8) Claims Appendix: Claims On Appeal

1. (rejected) A method for producing polyhydroxyalkanoates comprising providing organisms selected from the group consisting of bacteria, plants, and yeast, which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase, wherein the organisms are genetically engineered to express enzymes, which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase, which can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, and culturing the organisms under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

2. (rejected) The method of claim 1 wherein the diol is 1,6-hexanediol and the hydroxyalkanoate monomer is 6-hydroxyhexanoate.

3. (rejected) The method of claim 1 wherein the diol is 1,5-pentanediol and the hydroxyalkanoate monomer is 5-hydroxyvalerate.

4. (rejected) The method of claim 1 wherein the diol is 1,4-butanediol and the hydroxyalkanoate monomer is 4-hydroxybutyrate.

6. (rejected) The method of claim 1 wherein the diol is 1,2-ethanediol and the hydroxyalkanoate monomer is 2-hydroxyethanoate.

7. (rejected) The method of claim 1 wherein the diol is 1,2-propanediol and the hydroxyalkanoate monomer is 2-hydroxypropionate.

8. (rejected) The method of claim 1 wherein the organism expresses polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase.

9. (rejected) The method of claim 8 wherein the organism is selected from the group consisting of *Escherichia coli*, *Ralstonia eutropha*, *Klebsiella* spp., *Alcaligenes latus*, *Azotobacter* spp., and *Comamonas* spp.

10. (rejected) A system for making polyhydroxyalkanoates comprising organisms selected from the group consisting of bacteria, plants, and yeast , which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase, wherein the organism is genetically engineered to express enzymes, which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase, wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate, wherein the monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da.

Claim Support Section

1. (rejected) A method for producing polyhydroxyalkanoates comprising providing organisms selected from the group consisting of bacteria, plants, and yeast, **{p. 5, *ll* 18-21}** which express enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase, **{p. 5, *ll* 1-5}** wherein the organisms are genetically engineered to express enzymes **{p. 3, *ll* 15-18}**, which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase **{p. 4, *ll* 2-3, p. 5, *l* 18 to p. 6, *l* 28, p. 16, *l* 20 to p. 19, *l* 4}**, which can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate,**{p. 2 *l* 25 to p, 3 *l* 3, original claims 11 and 12}** and culturing the organisms under conditions wherein the hydroxyalkanoate monomers are polymerized by the activity of a PHA synthase enzyme **{p. 4, *ll* 14-18, original claims 1 and 11, p. 9, *l* 28 to p. 20 *l* 6}** to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da **{original claim 11, . p. 9, *l* 28 to p. 20 *l* 6}**

2. (rejected) The method of claim 1 wherein the diol is 1,6-hexanediol **{p. 2, l 28; p. 9, ll 17-18}** and the hydroxyalkanoate monomer is 6-hydroxyhexanoate **{p. 2, l 28; original claim 2}** .

3. (rejected) The method of claim 1 wherein the diol is 1,5-pentanediol **{p. 2, l 27; p. 9, ll 17-18; original claim 3** and the hydroxyalkanoate monomer is 5-hydroxyvalerate **{p. 2, l 27; p. 9, ll 17-18; original claim 3}**.

4. (rejected) The method of claim 1 wherein the diol is 1,4-butanediol **{p.2 ,l 26; p. 9. ll 17-18; Figure 1; original claim 4}** and the hydroxyalkanoate monomer is 4-hydroxybutyrate **{p.2 ,l 26; p. 9. ll 17-18; Figure 1; original claim 4}**.

6. (rejected) The method of claim 1 wherein the diol is 1,2-ethanediol **{p. 3, l 3; p. 9, ll 17-18; original claim 6}**and the hydroxyalkanoate monomer is 2-hydroxyethanoate. **{p. 3, l 3; p. 9, ll 17-18; original claim 6}**

7. (rejected) The method of claim 1 wherein the diol is 1,2-propanediol **{p. 3, l 1; p. 9, ll 17-18; original claim 7}** and the hydroxyalkanoate monomer is 2-hydroxypropionate **{p. 3, l 1; p. 9, ll 17-18; original claim 7}**.

8. (rejected) The method of claim 1 wherein the organism expresses polynucleotides which encode aldehyde dehydrogenase and diol oxidoreductase **{p. 4, ll 2-3; original claim 8}**.

9. (rejected) The method of claim 8 wherein the organism is selected from the group consisting of *Escherichia coli* **{p. 3, l 19; p.6, l 19; original claim 9}**, *Ralstonia eutropha*, {p. 3, l 20; p. 5, l 6-7; p. 11, ll 24; p. 12, ll 11; original claim 9} *Klebsiella* spp.**{p. 6, ll 12-17; original claim 9}**, *Alcaligenes latus* **{p. 3, ll 20-21; original c aim 9}**, *Azotobacter* spp. **{original c aim 9}**, and *Comamonas* spp. **{p. 1, l 20; original c aim 9}**

10. (rejected) A system for making polyhydroxyalkanoates comprising organisms selected from the group consisting of bacteria, plants, and yeast **{p. 5, *ll* 18-21}**, which express

enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β-ketothiolase, acetoacetyl-CoA reductase, and PHA synthase **{p. 5, *ll* 1-5}**, wherein the organism is genetically engineered to express enzymes **{p. 3, *ll* 15-18}**, which are active in bacteria or plants, selected from the group consisting of diol oxidoreductase and aldehyde dehydrogenase **{p. 4, *ll* 2-3, p. 5, *l* 18 to p. 6, *l* 28, p. 16, *l* 20 to p. 19, *l* 4}**, wherein the enzymes expressed by the organisms can convert diols into hydroxyalkanoate monomers selected from the group consisting of 4-hydroxybutyrate, 2-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, 6-hydroxyhexanoate, 2-hydroxyethanoate, 2-hydroxypropionate, and 3-hydroxyhexanoate **{p. 2 *l* 25 to p, 3 *l* 3, original claims 11 and 12}**, wherein the monomers are polymerized by the activity of a PHA synthase enzyme to form polyhydroxyalkanoates having a weight-average molecular weight (Mw) of at least 300,000 Da. **{original claim 11, . p. 9, *l* 28 to p. 20 *l* 6}**

(9) Evidence Appendix

None

(10) Related Proceedings Appendix

None